iPS cells reveal stem cell origin of disease

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A new *Nature* paper from CIRM grantees at Stanford University once again shows the value of reprogrammed iPS cells in understanding disease. Scientists can't develop a therapy for a disease if they don't know what it is going wrong. In many cases, iPS cells have provided the first ever way of peering into diseased cells and finding which proteins and genes need fixing.

In this case, the disease in question is dyskeratosis congenita, in which the caps on the ends of chromosomes shorten abnormally and causes a wide variety of symptoms ranging from abnormal skin pigmentation and nail growth to lung scarring, bone marrow failure and cancer. The question has been why people with the same disease can have such dramatically different symptoms, and what to do about those symptoms.

The Stanford group reprogrammed the skin cells of people with the disease into embryonic-like iPS cells. They knew people with the disease made low levels of a protein conglomerate called telomerase, which is responsible for maintaining those chromosomal caps. What they found in those iPS cells is that the more severe a person's disease, the less telomerase their iPS cells made.

A Stanford press release quotes senior author Steven Artandi:

"We were very surprised to find such a clear correlation between the quantity of functional telomerase, the severity of the cellular defect and the severity of the patient's clinical symptoms," said associate professor of medicine Steven Artandi, MD, PhD. "Our work suggests that, in patients with dyskeratosis congenita, tissue stem cells are losing their ability to self-renew throughout the body. This is a new, unifying way to think about this disease, and it has important implications for many other conditions."

Reprogrammed iPS cells can normally divide indefinitely in the lab. The iPS cells made from people with dyskeratosis congenita eventually stopped being able to divide and instead matured into the body's cell types. The researchers think this means the disease symptoms occur when stem cells in the tissues lose their ability to divide indefinitely. With no stem cells in the bone marrow, skin or other organs, the person's body can't repair damage or maintain tissues. That seems to be what causes symptoms of dyskeratosis congenita.

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